Neuropathic Pain: Pathophysiology and Treatment

Per T. Hansson
Howard L. Fields
Raymond G. Hill
Paolo Marchettini
Editors

Progress
in Pain Research
and Management
VOLUME 21

INTERNATIONAL
ASSOCIATION
FOR THE
STUDY OF PAIN

Progress in Pain Research and Management
Volume 21

Neuropathic Pain: Pathophysiology and Treatment

Editors

Per T. Hansson, MD, PhD, DDS

Neurogenic Pain Unit, Multidisciplinary Pain Center,
Department of Rehabilitation Medicine,
Karolinska Hospital, Stockholm, Sweden

Howard L. Fields, MD, PhD

Department of Neurology, University of California,
San Francisco, California, USA

Raymond G. Hill, PhD

The Neuroscience Research Centre, Merck Sharp and Dohme,
Terlings Park, Essex, United Kingdom

Paolo Marchettini, MD

Pain Medicine Center, Scientific Institute
and Hospital San Raffaele, Milan, Italy

IASP PRESS® • SEATTLE

Timely topics in pain research and treatment have been selected for publication, but the information provided and opinions expressed have not involved any verification of the findings, conclusions, and opinions by IASP®. Thus, opinions expressed in *Neuropathic Pain: Pathophysiology and Treatment* do not necessarily reflect those of IASP or of the Officers and Councillors.

Library of Congress Cataloging-in-Publication Data

Neuropathic pain : pathophysiology and treatment / editors, Per T. Hansson ... [et al.].
p. ; cm. -- (Progress in pain research and management ; v. 21)
Includes bibliographical references and index.
ISBN 0-931092-38-8 (alk. paper)
1. Nervous system--Pathophysiology. 2. Neuralgia. 3. Central pain. I. Hansson, Per, 1955- II Series.
[DNLM: 1. Neuralgia--physiopathology. 2. Neuralgia--therapy. WL 544 N4946 2001]
RC347.N4797 2001
616.8'047--dc21

2001026397

Published by:

IASP Press
International Association for the Study of Pain
909 NE 43rd St., Suite 306
Seattle, WA 98105 USA
Fax: 206-547-1703
www.painbooks.org

Printed in the United States of America

Contributing Authors

Miroslav Backonja, MD *Department of Neurology, University of Wisconsin, Madison, Wisconsin, USA*

Mark Baker, PhD *Department of Biology, University College London, London, United Kingdom*

Ralf Baron, Dr med *Neurology Clinic, University of Kiel, Kiel, Germany*

Joel A. Black, PhD *Department of Neurology and PVA-EPVA Neuroscience Research Center, Yale University School of Medicine, New Haven, Connecticut; and Rehabilitation Research Center, Veterans Affairs Hospital, West Haven, Connecticut, USA*

Mario Campero, MD *Department of Neurology, University of Chile, Santiago, Chile*

Theodore R. Cummins, PhD *Department of Neurology and PVA-EPVA Neuroscience Research Center, Yale University School of Medicine, New Haven, Connecticut; and Rehabilitation Research Center, Veterans Affairs Hospital, West Haven, Connecticut, USA*

Sulayman Dib-Hajj, PhD *Department of Neurology and PVA-EPVA Neuroscience Research Center, Yale University School of Medicine, New Haven, Connecticut; and Rehabilitation Research Center, Veterans Affairs Hospital, West Haven, Connecticut, USA*

Anthony H. Dickenson, PhD *Department of Pharmacology, University College London, London, United Kingdom*

Howard L. Fields, MD, PhD *Department of Neurology, University of California, San Francisco, California, USA*

Per T. Hansson, MD, PhD, DDS *Neurogenic Pain Unit, Multidisciplinary Pain Center, Department of Rehabilitation Medicine, Karolinska Hospital/Institute, Stockholm, Sweden*

Raymond G. Hill, PhD *The Neuroscience Research Centre, Merck Sharp and Dohme, Terlings Park, Essex, United Kingdom*

Wilfrid Jänig, Dr med *Institute of Physiology, University of Kiel, Kiel, Germany*

Troels S. Jensen, MD *Department of Neurology, Aarhus University Hospital, Aarhus, Denmark*

Marco Lacerenza, MD *Pain Medicine Center, Scientific Institute and Hospital San Raffaele, Milan, Italy*

Josephine Lai, PhD *Department of Pharmacology, Health Sciences Center, University of Arizona, Tucson, Arizona, USA*

Bengt Linderoth, MD, PhD *Department of Neurosurgery, Karolinska Hospital/Institute, Stockholm, Sweden*

T. Philip Malan, Jr., MD, PhD *Departments of Pharmacology and Anesthesiology, Health Sciences Center, University of Arizona, Tucson, Arizona, USA*

Paolo Marchettini, MD *Pain Medicine Center, Scientific Institute and Hospital San Raffaele, Milan, Italy*

Elizabeth A. Matthews, BSc *Department of Pharmacology, University College London, London, United Kingdom*

Björn A. Meyerson, MD, PhD *Department of Neurosurgery, Karolinska Hospital/Institute, Stockholm, Sweden*

Turo J. Nurmikko, MD, PhD *Pain Research Institute, Department of Neurological Science, University of Liverpool, Liverpool, United Kingdom*

José Ochoa, MD, PhD *Neuromuscular Unit, Good Samaritan Hospital and Medical Center, and Oregon Health Sciences University, Portland, Oregon, USA*

Kenji Okuse, PhD *Department of Biology, University College London, London, United Kingdom*

Michael H. Ossipov, PhD *Department of Pharmacology, Health Sciences Center, University of Arizona, Tucson, Arizona, USA*

Frank Porreca, PhD *Departments of Pharmacology and Anesthesiology, Health Sciences Center, University of Arizona, Tucson, Arizona, USA*

Michael C. Rowbotham, MD *Pain Clinical Research Center, University of California, San Francisco, California, USA*

Jordi Serra, MD *Neuropathic Pain Unit, Sagrada Familia Clinic, Barcelona, Spain*

Søren H. Sindrup, MD *Department of Neurology, Odense University Hospital, and Department of Clinical Pharmacology, University of Southern Denmark, Odense, Denmark*

Claudia Sommer, MD *Department of Neurology, University of Würzburg, Würzburg, Germany*

Rie Suzuki, PhD *Department of Pharmacology, University College London, London, United Kingdom*

Todd W. Vanderah, PhD *Departments of Pharmacology and Anesthesiology, Health Sciences Center, University of Arizona, Tucson, Arizona, USA*

C. Peter N. Watson, MD, FRCPC *Department of Medicine, University of Toronto, Toronto, Ontario, Canada*

Stephen G. Waxman, MD, PhD *Department of Neurology and PVA-EPVA Neuroscience Research Center, Yale University School of Medicine, New Haven, Connecticut; and Rehabilitation Research Center, Veterans Affairs Hospital, West Haven, Connecticut, USA*

John N. Wood, DSc *Department of Biology, University College London, London, United Kingdom*

Preface

Pain in neuropathy has been extensively studied, both clinically and experimentally. Despite this multifaceted research approach we still face significant shortcomings in our ability to successfully treat patients with neuropathic pain, partly due to our inadequate knowledge of pathophysiological mechanisms related to its initiation and maintenance. Several animal models of neuropathic pain have been developed to facilitate the study of such mechanisms. To be able to apply what we have learned from these models to clinical neuropathic pain, we must address significant limitations of animal research related to painful neuropathy. For example, we can certainly accept the relevance of the various ways to induce neuropathy, but we are left with uncertainty regarding the presence of spontaneous or stimulus-evoked pain. Behavioral studies in animal models of neuropathy rely heavily on stimulus-induced reflex abnormalities such as extremity withdrawal latency or duration, and these may or may not reflect the conscious perception of stimulus-evoked pain in humans. An open discussion between clinicians/clinical scientists and animal researchers on the clinical relevance of animal models and sensory testing techniques in such models may aid in defining to what extent animal models mimic clinical neuropathic pain.

Initial inspiration for this book came from the attractive content of two symposia on neuropathic pain held in conjunction with the International Association for the Study of Pain's 9th World Congress in Vienna. In Como, Italy, symposium contributors focused on pharmacological treatment of ongoing and stimulus-evoked neuropathic pain, and in Seeon, Germany, participants addressed mechanism-based approaches to the treatment of neuropathic pain. These meetings suggested the timeliness of a cohesive volume summarizing the latest knowledge within crucial areas of neuropathic pain. Chapter authors were invited to concentrate on key issues regarding diagnosis and treatment as well as research related to pathophysiology, whether clinical or experimental. Most importantly, we chose to present a state-of-the-art review of research and clinical practice in the field, rather than simply to create a proceedings book of the symposia.

With this volume, editors and authors hope to provide the reader with a fundamental background as well as recently emerging information within the area of neuropathic pain. The book should assist health care professionals in providing high-quality patient care, including a more rational application of possible pain mechanisms and the latest information about effective

treatments. The content illustrates the potential value of current and future research efforts directed toward increased understanding of the pathophysiology of pain in neuropathy. Better understanding of the mechanisms underlying the different aspects of neuropathic pains holds the promise of treatment strategies that selectively target each mechanism. We hope this book will provide a ray of hope to the thousands of people suffering from the relentless assaults on their lives from neuropathic pain.

PER T. HANSSON, MD, PHD, DDS
HOWARD L. FIELDS, MD, PHD
RAYMOND G. HILL, PHD
PAOLO MARCHETTINI, MD

Contents

Neuropathic Pain: Pathophysiology and Treatment, Progress in Pain Research and Management, Vol. 21, edited by Per T. Hansson, Howard L. Fields, Raymond G. Hill, and Paolo Marchettini, IASP Press, Seattle, © 2001.

1

Aspects of Clinical and Experimental Neuropathic Pain: The Clinical Perspective

Per Hansson,[a] Marco Lacerenza,[b] and Paolo Marchettini[b]

[a]Neurogenic Pain Unit, Multidisciplinary Pain Center and Department of Rehabilitation Medicine, Karolinska Hospital/Institute, Stockholm, Sweden; [b]Pain Medicine Center, Scientific Institute and Hospital San Raffaele, Milan, Italy

Painful neuropathic conditions may accompany a lesion of the peripheral or central nervous system. Table I summarizes conditions that may be associated with pain. All types of neuropathic pain are projected to the innervation territory of the damaged nerve or pathway, according to the somatotopic organization of the primary somatosensory cortex. Examples of projected pain are pain localized to the amputated area in phantom pain or pain perceived in the ulnar part of the hand in ulnar nerve entrapment in the elbow. Nerve root compression from a herniated disk usually involves a combination of nociceptive pain in the area of the ruptured disk and neuropathic pain projected within the dermatome corresponding to the affected root(s). When the nociceptors innervating the perineurium (the endings of the nervi nervorum) are activated during inflammation or compression, the resulting pain is nociceptive and is mainly localized to the site of disturbance.

Painful neuropathies are characterized by spontaneous and/or abnormal stimulus-evoked pain. Evoked pain is defined as *allodynia* when caused by normally innocuous stimuli, usually light mechanical stimuli (Merskey and Bogduk 1994). Pain caused by normally innocuous stimuli is not unique to neuropathic pain; it may also occur in non-neuropathic conditions such as skin injury (e.g., sunburn), joint inflammation, and hysterical pain conditions. The mechanisms underlying allodynia in various clinical conditions are different, and a thorough medical history and examination will point to

Table I
Conditions in which neuropathic/neurogenic pain may appear

Peripheral
Traumatic (including iatrogenic) nerve injury
Ischemic neuropathy
Nerve compression/entrapment
Polyneuropathy (hereditary, metabolic, toxic, inflammatory, infectious, paraneoplastic, nutritional, in amyloidosis and vasculitis)
Plexus injury
Root compression
Stump and phantom pain after amputation
Herpes zoster/postherpetic neuralgia
Trigeminal and glossopharyngeal neuralgia
Cancer-related neuropathy (due to neural invasion of the tumor, surgical nerve damage, radiation-induced nerve damage, chemotherapy-induced neuropathy)
Central
Stroke (infarct or hemorrhage)
Multiple sclerosis
Spinal cord injury
Syringomyelia/syringobulbia
Epilepsy
Space-occupying lesions

the underlying cause. From a quality of life point of view, allodynia, especially dynamic mechanical allodynia, is highly disabling to affected subgroups of neuropathic pain patients.

In contrast to allodynia, *hyperalgesia* is defined as increased pain intensity evoked by normally painful stimuli (Merskey and Bogduk 1994). Neuropathic pain states are also often associated with nonpainful abnormal spontaneous and evoked sensory phenomena such as paresthesia and dysesthesia.

For the vast majority of neuropathic diagnostic entities the percentage of subjects reporting neuropathic pain is not precisely known. However, an estimated 5% of patients with traumatic nerve injury suffer from pain (Sunderland 1993). Further, about 8% of stroke patients suffer from central neuropathic pain (Andersen et al. 1995), as do 28% of patients with multiple sclerosis and 75% of patients with syringomyelia (Boivie 1999). Detailed studies in patients with central pain due to stroke (Boivie et al. 1989; Leijon et al. 1989) or multiple sclerosis (Boivie et al. 1989; Osterberg et al. 1994) have identified a common denominator in central pain: somatosensory examination typically reveals signs of involvement of the spino- (trigemino-) thalamocortical system, resulting in altered sensitivity to temperature and/or

pain stimuli. The painful condition is not consistently related to alterations in other somatosensory channels or in the motor system (Leijon et al. 1989). No common denominator has been identified in peripheral neuropathic pain states, although small myelinated and unmyelinated fibers are probably involved in most cases because neuropathies with predominant involvement of large myelinated fibers often are not painful (Asbury 1990). We still do not know why seemingly similar nerve injuries can be painful in some cases and painless in others. In addition, no systematic studies in neuropathic pain patients have investigated the correlation between the intensity of symptoms and the nature and severity of the nerve injury. In highly specialized units for neuropathic pain, patients with pain in areas with partial nerve injury greatly outnumber patients with complete deafferentation and pain. This finding could imply a lower incidence of painful sequelae in total deafferentation or may simply reflect the lower frequency of total deafferentation in the population of neuropathic pain patients.

Current drug and nondrug therapies for chronic neuropathic pain, based on observations from clinical studies, clinical anecdotes, and experimental findings, offer substantial pain relief to no more than half of the affected patients (Hansson 1994b). In the vast majority of cases, chronic neuropathic pain cannot be successfully treated using conventional analgesics and is resistant to oral opioids. Opioid sensitivity in neuropathic pain is a controversial issue within the scientific community (Arnér and Meyerson 1988; Kupers et al. 1991; Rowbotham et al. 1991). The array of therapeutic agents is multifaceted (Table II), but is efficacious, to some extent, in only about half of the patients. No systematic studies have evaluated drug combinations in different neuropathic pain conditions. In clinical practice it is important to inform the patient and relatives, early on, about the difficulties related to treatment, without creating despair, explaining that most patients who benefit from treatment achieve only partial relief of pain. Unrealistic expectations regarding treatment outcome may deprive the patient of enjoying partial relief. There is no predictor for the response of an individual patient to a specific intervention, and the treatment strategy is based on trial and error. Effective new treatment strategies are desperately needed.

DEFINITION OF NEUROGENIC/NEUROPATHIC PAIN

The International Association for the Study of Pain (Merskey and Bogduk 1994) defines neurogenic pain as "Pain initiated or caused by a primary lesion or dysfunction or transitory perturbation in the peripheral or central nervous system." Neuropathic pain is a subentity where "transitory perturbation" is

Table II
Proposed therapies for neuropathic pain

Pharmacological Therapies
Antidepressants (amitriptyline, maprotiline, selective serotonin reuptake inhibitors)
Antiepileptics (gabapentin, carbamazepine, clonazepam, lamotrigine, topiramate, phenytoin)
Local anesthetics and mexiletine
Baclofen
Clonidine
Ketamine
Dextrorphan
Tramadol
Guanethidine
Opioids (morphine, methadone, ketobemidone, fentanyl)
Neurostimulation Techniques
Transcutaneous electrical nerve stimulation
Spinal cord stimulation
Motor cortex stimulation
Deep brain stimulation
Surgical Interventions
Decompression
Neuroma removal
Neurotomy
Glycerol injection
Radiofrequency nerve/root lesion
Dorsal root entry zone lesion
Cordotomy
Stereotactic radiosurgery

omitted. The inclusion of "dysfunction" in the definition may be a source of confusion because it allows nociceptive and psychogenic conditions to be improperly diagnosed as neurogenic/neuropathic. A neurobiological response to nerve injury, such as alteration of sodium channel expression or peripheral and central sensitization, might be considered "dysfunctions" of the nervous system. There is evidence for sensitization of primary afferents in some neuropathic pain patients, such as subgroups of patients with postherpetic neuralgia (Rowbotham and Fields 1996; Petersen et al. 2000), but also in nociceptive pain states such as rheumatoid arthritis. Central sensitization, expressing itself as allodynia to mechanical and/or thermal stimuli, is a prominent sign of both clinical neurogenic/neuropathic and nociceptive pain conditions. Thus, if such alterations are accepted as "dysfunctions" of

the nervous system, the term is too broad to be part of the definition of neurogenic/neuropathic pain. Therefore, and for the sake of simplicity, we suggest amending the definition of neuropathic pain to: "pain due to a primary lesion of the peripheral or central nervous system." The use of "neurogenic pain" could be confined to classical neurological painful conditions such as trigeminal and glossopharyngeal neuralgia where neuropathy may be difficult to demonstrate. Symptom irreversibility is not critical because in long-standing conditions pain may subside over time.

Clinical neurologists commonly encounter patients with pain and other symptoms and signs suggesting abnormalities within the somatosensory system that cannot be linked to an identifiable structural lesion of the nervous system. Such symptoms are commonly labeled as "nonorganic," based on the assumption that symptoms and signs are "psychogenic" in nature. Psychogenicity is clearly an expression of brain function, and symptoms most likely result from biochemical and/or physiological alterations. Abnormal modification of inhibitory or facilitatory systems might be responsible for the loss or amplification of somatosensory or other functions. Modulatory systems may also contribute to complex regional pain syndrome type I and chronic pain localized to musculoskeletal structures. In addition, processing of nociceptive inputs is attenuated across sleep stages (Lavigne et al. 2000). Clinical conditions with spontaneous and abnormal induced pain may result from altered central modulation within the somatosensory system. This phenomenon has been suggested to occur in conditions such as fibromyalgia (Kosek et al. 1996) and osteoarthritis (Kosek and Ordeberg 2000). While we emphasize that these sensory dysfunctions are not due to structural lesions of classical neurological pathways, we propose that they are organic and may be due to abnormal activation of facilitatory or inhibitory systems or pain projection pathways. Abnormal frontal lobe activity has so far been described in only a few patients with neurological symptoms from hysteria (Tiihonen et al. 1995; Marshall et al. 1997). Patients with this kind of sensory disorder require meticulous neurological and psychological assessment and possibly pharmacological testing to determine appropriate treatments aimed at recovering inhibition or erasing abnormal facilitation. Careful diagnosis is necessary to differentiate between traditional "organic" neurological disorders and "functional-organic" conditions and to prevent invasive, potentially harmful interventions in the latter category (Ron 1994). Somatization in depression is known to be a condition at high risk for iatrogenesis (Kouyanou et al. 1998; Marchettini et al. 2000), as is Munchausen's syndrome (Wallace and Fitzmorris 1978). The category of "functional-organic" conditions should include patients diagnosed with hysteria or with psychosomatic or somatoform disorders that are considered

unconscious dysfunctions. Malingering subjects should not be included in this category.

DIAGNOSTIC WORK-UP

Neuropathic pain is part of the neurological disease spectrum, and classical diagnostic criteria apply. The first step in the diagnostic work-up is taking a meticulous medical history, exploring the onset of pain and its possible association with current diseases, trauma, and surgery. The physician should explore the temporal aspects of the painful condition, which can lead to a specific diagnosis in a few neurogenic pain conditions, i.e., trigeminal and glossopharyngeal neuralgia. Other neuropathic pain conditions have no distinctive temporal profile but are continuous, sometimes with superimposed intermittent or paroxysmal painful or nonpainful symptoms. The presence of stimulus-evoked pain, often as disabling for the patient as spontaneous pain, should be carefully identified. Neuropathic pain conditions are often associated with unfamiliar symptom qualities that can be difficult for the patient to communicate. To enhance communication, the examining physician should reassure the patient that the symptoms are common expressions of such conditions.

The literature does not report consistent pathognomonic pain descriptors in peripheral or central neuropathic pain, and each patient may use several sensory-discriminative descriptors. Leijon and coworkers (1989) reported no common denominators from their series of patients with central pain. However, burning, sometimes shock-like or electrical pain in conjunction with numbness, tingling, and pins and needles projected to a cutaneous area is highly indicative of a neuropathic condition. Importantly, aching pain does not rule out the possibility of a neuropathic basis and may be a frequent complaint in patients with central pain due to multiple sclerosis (Osterberg et al. 1994) or syringomyelia (Boivie 1999). The pain distribution, with few exceptions (see below), matches the level of the lesion. A neuroanatomical distribution correlating with the site of the lesion supports the diagnosis of neuropathic pain and should be explored thoroughly using a pain drawing completed by the patient (Fig. 1a–e).

Physicians examining neuropathic pain patients should evaluate sensory, motor, and autonomic signs to confirm or reject the suspected anatomical localization of the lesion extracted from a careful history. Because pain is part of the somatosensory system, the diagnosis of painful neuropathy rests heavily on the demonstration of sensory abnormalities in the area corresponding to the innervation territory of the damaged nerve, plexus,

root, or central pathway. A careful bedside examination of somatosensory functions, using an array of instruments (Hansson 1994a) to explore the entire spectrum of fibers/pathways, is crucial because sensory aberrations may be confined to a single or few sensory modalities. The examination of somatosensory function should be the final part of the diagnostic work-up, and should be guided by a tentative diagnosis based on the information collected up to that point. The outcome of the bedside examination is often a sufficient basis for diagnosis. Since the distribution of sensory abnormalities matches the innervation territory of the damaged nervous structure, the borders of the area of sensory dysfunction should be carefully mapped using different modalities. If the sensory examination is started within the area of dysfunction and is directed toward the normal areas around it, the area of abnormality will appear larger than when testing from the outside in. The reason for this discrepancy is the inherent reaction time that it takes for the patient to perceive and report alterations in sensations. In clinical practice, we recommend testing from the inside out to explore an area of sensory deficit, but from the outside in to explore a territory with positive sensory phenomena, such as mechanical or thermal allodynia or hyperalgesia, so as to minimize the duration of painful stimulation.

Extraterritorial spread of pain and/or sensory dysfunction should be accepted as evidence of central sensitization only after careful differential diagnosis to rule out non-neurological conditions. Extraterritorial spread, seen only occasionally, usually develops after a period of proper distribution of signs and symptoms and may in some cases be interpreted as variations in the innervation territories of nerves or roots (Tal and Bennett 1994; Sotgiu and Biella 1995; Lacerenza et al. 1996) (Fig. 1e). The extension of the extraterritorial spread varies over time, is arbitrary, and cannot be quantified. Sound clinical reasoning should be the basis for diagnosis.

Regarding the somatosensory examination, specific characteristics apply to true neuropathic conditions, i.e., the modality profile and borders of abnormalities are reproducible during one examination. To further explore the somatosensory status, psychophysical quantitative somatosensory testing techniques (Hansson 1994a) may be added to assess perception threshold, so as to complement standard clinical neurophysiological methods, which fall short in demonstrating pathology of the small fiber system and in revealing positive phenomena such as dynamic mechanical allodynia (Verdugo and Ochoa 1992).

Motor dysfunction, such as tremor and weakness, in the absence of damage to the motor system, is either a somatomotor reflex, a protective behavior, or a psychologically conditioned overlay. Autonomic signs may be a direct consequence of the nerve injury, or a spinal/supraspinal reflex to

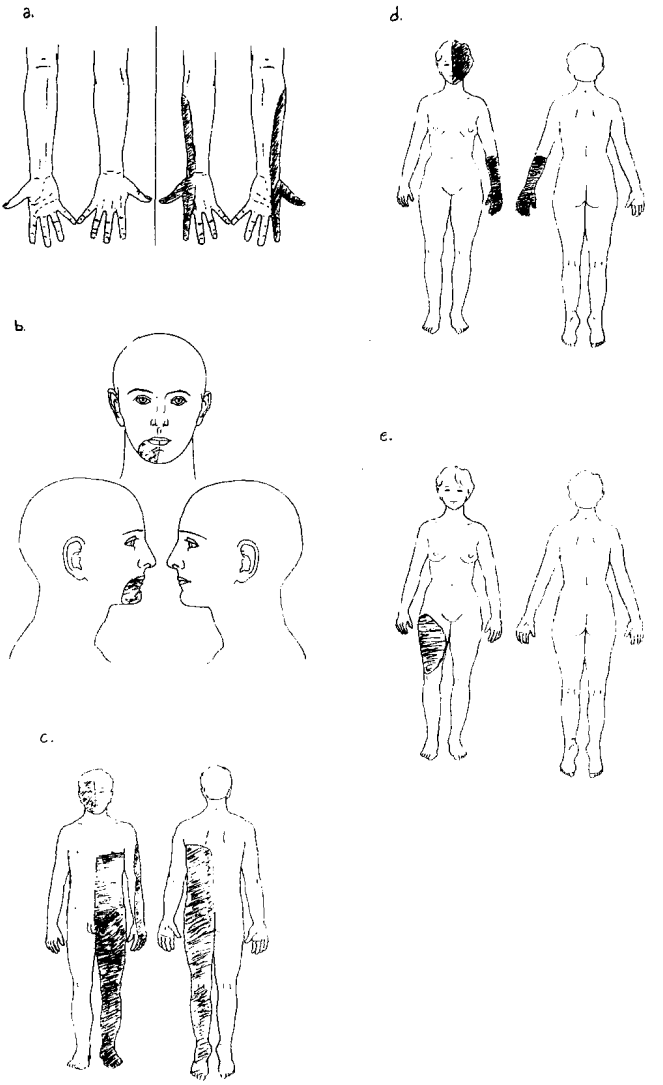

Fig. 1. Drawings from five different patients with neuropathic pain, emphasizing their usefulness in defining the neuroanatomically correlated distribution of projected pain and other sensory symptoms. Symptomatic areas are shaded. (a) A 30-year-old male patient with a herniated disk at the C5–C6 level and a painful rhizopathy distributed in the C6 dermatome of the left arm. On the whole-body drawing (not shown), the patient also indicated pain in the neck. (b) A 44-year-old male patient with a traumatic fracture of the right corpus of the mandible during a car accident and a lesion of the inferior alveolar nerve. The patient suffers from ongoing pain and aggravation of pain during tactile stimuli in an area corresponding to the innervation territory of the mental nerve, the most peripheral part of the inferior alveolar nerve. (c) A 40-year-old male patient with a brainstem infarct (Wallenberg's syndrome) on the right side. In the right side of